PRODUCT MONOGRAPH

PrSANDOZ DICLOFENAC

Diclofenac Sodium Suppositories

50 mg and 100 mg

THERAPEUTIC CLASSIFICATION

Anti-inflammatory - Analgesic

Sandoz Canada Inc.
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ACTIONS AND CLINICAL PHARMACOLOGY

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Although the mode of action is not fully known, it does not act through the pituitary-adrenal axis. By interfering with the action of prostaglandin synthetase diclofenac sodium inhibits prostaglandin synthesis. Diclofenac's actions may be partially explained by this inhibitory effect.

From a clinical efficacy standpoint, 75 mg of diclofenac sodium has an activity similar to that of 3.6 g of acetylsalicylic acid (ASA).

Diclofenac sodium is similar in activity to equivalent doses of indomethacin (75-150 mg daily). However, at these doses, diclofenac causes less CNS side effects.

Although diclofenac sodium has been found to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders of the types listed it does not alter the course of the underlying disease.

Two bioavailability studies were performed using human volunteers. The rate and extent of absorption after a single rectal administration of Voltaren® 50 mg and SANDOZ DICLOFENAC

50 mg suppositories, and Voltaren® 100 mg and SANOZ DICLOFENAC 100 mg suppositories, were measured and compared. The results obtained can be summarized as follows:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

DICLOFENAC SODIUM

(50 mg suppositories)

From measured data

Parameter	**Geometric Mean Arithmetic Mean (C.V.%)**		**Ratio of Means (%)[A]**
	Test*	**Reference****	**Test/Reference**
AUC_t (ng.hr/mL)	1172.7 1214.1 (28)	1273.2 1316.8 (29)	92%
AUC_I (ng.hr/mL)	1220.1 1261.7 (28)	1329.2 1374.6 (29)	92%
C_{max} (ng/mL)	509.7 549.1 (37)	590.4 616.7 (30)	86%
T_{max} (hours)***	0.82 (58)	1.09 (48)	----
$T_{1/2}$ (hours)***	1.48 (53)	1.50 (51)	----
K_{el} ($hour^{-1}$)***	0.5763 (41)	0.5546 (38)	-----

* Test product was SANDOZ DICLOFENAC 50 mg Suppository (Sandoz)

** Reference product was Voltaren® 50 mg Suppository (Geigy, Canada)

*** These are arithmetic means (C.V.%)

^ Calculated using geometric means according to the formula: $e^{(\text{Sandoz (A)- Voltaren(B)})} \times 100\%$

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (C.V.%) only.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

DICLOFENAC SODIUM

(100 mg suppositories)

From measured data

Parameter	Geometric MeanArithmetic Mean (C.V.%)		Ratio of Means (%)[A]
	Test*	Reference**	Test/Reference
AUC_t (ng.hr/mL)	2624.2 2714.1 (27)	2484.3 2565.8 (26)	106%
AUC_I (ng.hr/mL)	2700.7 2787.6 (27)	2601.9 2691.5 (27)	104%
C_{max} (ng/mL)	1299.7 1393.7 (42)	1284.1 1341.1 (31)	101%
T_{max} (hours)***	0.68 (33)	0.94 (55)	----
$T_{1/2}$ (hours)***	1.63 (53)	1.84 (48)	----
K_{el} ($hour^{-1}$)***	0.5458 (47)	0.4833 (48)	----

* Test product was SANDOZ DICLOFENAC 100 mg Suppository (Sandoz)

** Reference product was Voltaren® 100 mg Suppository (Geigy, Canada)

*** These are arithmetic means (C.V.%)

[A] Calculated using geometric means according to the formula : $e^{(\text{Sandoz (A)- Voltaren(B)})} \times 100\%$

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (C.V.%) only.

PHARMACOKINETICS AND METABOLISM

Absorption

Suppositories have a more rapid onset, but slower rate of absorption than oral enteric-coated tablets. C_{max} is approximately 2/3 of that produced by an equivalent 50 mg enteric-coated tablet oral dose. T_{max} occurs within 1 hour. The unchanged diclofenac plasma AUC values for rectal administration are within the range of values produced by equivalent oral enteric-coated tablet doses. Since about half the active substance is metabolized during its first passage through the

liver, "first pass" effect, the area under the concentration curve (AUC) following rectal administration is about half as large as it is following a parenteral dose of equal size, and is similar to that observed from the oral administration of diclofenac tablets.

Distribution

Diclofenac sodium is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.12 to 0.17 L/kg. Single-dose (oral or i.m.) studies in rheumatoid patients with joint effusions have shown that diclofenac is distributed to the synovial fluid, where T_{max} occurs 2 to 4 hours after plasma t_{max}. Synovial fluid concentrations exceed plasma levels within 4 to 6 hours of administration. This elevation above plasma concentrations can be maintained for up to 12 hours. The synovial fluid elimination half-life is at least 3 times greater than that for plasma.

Biotransformation

3'-, 4'-, 5-hydroxy, 4'-5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac are produced when diclofenac undergoes single and multiple hydroxylation and methoxylation. These phenolic metabolites, which are largely inactive, are mostly converted to glucuronide conjugates, as is the parent compound.

Elimination

Plasma clearance of diclofenac is 263 ± 56 mL/minute. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces.

The mean terminal drug half-life in plasma is 1.8 hours after oral doses of diclofenac tablets. More than 90% of an oral dose is accounted for in elimination products within 72 hours. About 1% of an oral dose is excreted unchanged in urine.

Special Populations

- **Renal Impairment**

  A single dose pharmacokinetic study in patients with varying degrees of renal dysfunction, as measured by creatinine clearance rates ranging from 3 mL/minute to 42 mL/minute, suggests that moderate renal impairment does not affect the elimination rate of unchanged diclofenac from plasma but that it may reduce the elimination rate of the metabolites of the drug. In one

patient with a creatinine clearance of <10 mL/minute, the theoretical steady-state plasma levels of metabolites (normally devoid of pharmacological activity) were about 4 times higher than those in normal subjects, with metabolites cleared through the bile. Caution is advised while administering diclofenac sodium to patients with impaired kidney function, even though no accumulation of pharmacologically active substance seems to occur.

- **Hepatic Impairment**

  In a study of 10 patients with impaired hepatic function (chronic hepatitis and nondecompensated cirrhosis) receiving a single oral dose of 100 mg, the kinetics and metabolism of diclofenac were the same as in patients without liver disease.

- **Geriatrics**

  The ability of elderly subjects to absorb, metabolize and excrete diclofenac sodium does not appear to differ significantly from those of young subjects.

INDICATIONS

Diclofenac sodium is indicated for the symptomatic treatment of rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

CONTRAINDICATIONS

The following are contraindications to the use of diclofenac sodium:

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

- Known or suspected hypersensitivity to the drug or other nonsteroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind.

Diclofenac sodium should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid

reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- Significant hepatic impairment or active liver disease.

- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

- Diclofenac sodium is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

- Suppositories are contraindicated in patients with any inflammatory lesions of the rectum or anus and in patients with a recent history of rectal or anal bleeding.

WARNINGS

Gastrointestinal system (GI)

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, **sometimes severe and occasionally fatal** can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including diclofenac sodium.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases.

The incidence of these complications increases with increasing dose.

Diclofenac sodium should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, diclofenac sodium should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients **not** at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagulant use have been associated with increased risk.

Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

Use in the Elderly

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs): the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less

tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower oesophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (See PRECAUTIONS).

Cross-sensitivity

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

Aseptic Meningitis

In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Use in pregnancy, labour and lactation

Diclofenac sodium readily crosses the placental barrier. The safety in pregnancy and lactation has not been established and its use is, therefore, not recommended. It should only be used during pregnancy for the most compelling reasons, and then only at the lowest effective dose. As with other prostaglandin inhibitors, this applies particularly to the last 3 months of pregnancy, because of the possibility of uterine inertia and/or premature closing of the ductus arteriosus.

The highest diclofenac level observed in the breast milk of 6 patients receiving oral diclofenac sodium doses of 3x50 mg day 1, followed by 2x50 mg on day 2, was less than 5 ng/g. By extrapolation, an infant of 3 kg, consuming 500 g/day of breast milk (with a maximum concentration of 5 ng/g), would receive less than 0.83 mcg/kg/day of diclofenac sodium. On the other hand, in 1 patient on long-term treatment with diclofenac sodium 150 mg daily, a level of 100 ng/mL (100 ng/g) was measured in breast milk; by extrapolation, an infant of 3 kg consuming 500 g/day of breast milk would receive less than 17 mcg/kg/day of diclofenac sodium.

Use in children

Diclofenac sodium is not recommended in children under 16 years of age. Safety and dosages for the pediatric age group have not been established.

Occupational Hazards

CNS: Headache, dizziness, light-headedness, and mental confusion have been reported following therapy. Patients should be made aware that these side effects may occur, and be cautioned against operating machinery and/or motor vehicles should they experience any of these.

PRECAUTIONS

Diclofenac sodium should not be used concomitantly with diclofenac potassium since both exist in plasma as the same active organic ion.

Gastrointestinal system

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of diclofenac sodium therapy when and if these adverse reactions appear.

Renal function

Long term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the

pre-treatment state.

Diclofenac sodium should be used with great caution in patients with impaired renal function, since it and its metabolites are eliminated primarily (60%) by the kidneys (see **PHARMACOLOGY**). In patients with impaired renal function lower doses of diclofenac should be considered. Urine output, serum urea, and serum creatinine should be carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Genitourinary tract

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with diclofenac sodium **must be stopped immediately** to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic function

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with nonsteroidal anti-inflammatory drugs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance

Fluid retention and edema have been observed in patients treated with diclofenac sodium. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Diclofenac sodium should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when diclofenac sodium is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Patients on long-term diclofenac sodium treatment should have their hemopoietic system evaluated periodically. Bone marrow functional abnormalities, although rare, could have severe consequences. Periodic hematologic examinations (CBC and blood film examination) can detect anaemia or blood dyscrasias secondary to possible gastrointestinal tract or bone marrow toxicity.

Infection

In common with other anti-inflammatory drugs, diclofenac sodium may mask the usual signs of infection.

Ophthalmology

Blurred and/or diminished vision has been reported with the use of diclofenac sodium and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Central nervous system

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of diclofenac sodium. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Hypersensitivity reactions

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without prior exposure to the drug. Careful questioning with respect to a patient history of asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs is important before initiating therapy.

INFORMATION PHYSICIANS SHOULD PROVIDE TO PATIENTS:

See **INFORMATION FOR THE PATIENT.**

DRUG INTERACTIONS

Acetylsalicylic acid (ASA)

Serum levels of diclofenac may be reduced when the two drugs are taken simultaneously. The bioavailability of ASA is reduced by the presence of diclofenac. Although these pharmacokinetic interactions do not appear to be clinically relevant, there is no proven advantage in using these two medications together.

Digoxin

Diclofenac may increase the plasma concentration of digoxin. Dosage adjustment may be required.

Anticoagulants

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases

the risk of GI adverse events such as ulceration and bleeding.

Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of diclofenac sodium with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Oral hypoglycemics

Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac. However, there have been isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac, which necessitated changes in the dosage of hypoglycemic agents.

Diuretics

NSAIDs have been reported to decrease the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels.

Anti-hypertensives

Like other NSAIDs, diclofenac can reduce the antihypertensive effects of propranolol and other β-blockers, as well as other antihypertensive agents.

Glucocorticoids

Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

NSAIDs

The use of diclofenac sodium in addition to any other NSAID, including those over-the-counter ones (such as ASA and Ibuprofen) is not recommended due to the possibility of additive side effects.

Methotrexate

Caution should be exercised when NSAIDs are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing toxicity.

Lithium

Since diclofenac affects lithium renal clearance, lithium plasma concentrations will increase when administered concomitantly with diclofenac. Dosage adjustment of lithium may be required.

Cyclosporine

Nephrotoxicity of cyclosporine may be increased because of the effect of NSAIDs on renal prostaglandins.

Quinolone antibacterials

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

CLINICAL LABORATORY TESTS

Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, and are unlikely to be clinically important.

Persistently abnormal or worsening renal, hepatic or haematological test values should be followed up carefully since they may be related to therapy.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

The adverse reactions reported and their relative frequency are summarized in tabular form at the end of this section.

Administration of the suppositories may occasionally give rise to local irritation, rarely local bleeding and exacerbation of hemorrhoids.

ADVERSE REACTION FREQUENCY SUMMARY

Effects	Occasional Incidence Level >1-10%	Rare Incidence Level >0.001-1%	Isolated Cases Incidence Level <0.001%
Gastrointestinal	Epigastric, gastric, or abdominal pain, abdominal cramps, nausea, dyspepsia, anorexia, diarrhea, vomiting, flatulence.	Gastric and intestinal ulcerations (with or without bleeding or perforation), gastrointestinal bleeding (e.g. bloody diarrhea, melena, hematemesis).	Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), hyperacidity, stomatitis, glossitis, coated tongue, oesophageal lesions., diaphragm-like intestinal strictures, constipation, pancreatitis.
Hypersensitivity/Allergic		Hypersensitivity reactions, such as asthma in patients sensitive to ASA, (e.g. bronchospasm, anaphylactic/ anaphylactoid systemic reactions including hypotension).	Vasculitis, pneumonitis.
Central Nervous System	Dizziness, headache, vertigo.	Malaise, drowsiness, impaired concentration, tiredness.	Irritability, disturbances of sensation including paresthesia, convulsions, memory disturbance, disorientation, depression, anxiety, nightmares, tremor, psychotic reactions, insomnia, aseptic meningitis.
Special Senses			Vision disturbances (blurred vision, diplopia), impaired hearing, tinnitus, taste alteration disorders.
Cardiovascular System		Palpitation, angina, arrhythmias.	Exacerbation of cardiac failure, hypertension.
Dermatologic	Rash, pruritus.	Urticaria.	Bullous eruption, eczema, erythema, photosensitivity reactions, loss of hair, erythema multiform, Stevens-Johnson syndrome, Lyell Syndrome (toxic epidermal necrolysis); erythroderma (exfoliative dermatitis), purpura including allergic purpura.
Renal System		Oedema (facial, general, peripheral).	Acute renal failure, nephrotic syndrome, urinary abnormalities (e.g. haematuria and proteinuria), interstitial nephritis, papillary necrosis.
Haematologic System			Leukopenia, thrombocytopenia, agranulocytosis, hemolytic anaemia, aplasic anaemia, anaemia secondary to gastrointestinal bleeding.
Hepatic System	Elevation (≥ 3 times the upper normal limit) of serum aminotransferase enzymes (SGOT or AST, SGPT or ALT).	Liver function disorders including hepatitis (with or without jaundice).	Fulminant hepatitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific antidote for diclofenac sodium. In cases of overdosage, absorption should be prevented as soon as possible by the induction of vomiting, gastric lavage or treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression. Measures to accelerate elimination (forced diuresis, hemoperfusion, and dialysis) may be considered, but may be of limited use because of the high protein-binding and extensive metabolism of diclofenac sodium.

DOSAGE AND ADMINISTRATION

Adults

Rheumatoid arthritis and osteoarthritis: 50 or 100 mg may be given as a substitute for the last of the 3 oral daily doses. The maximum combined (tablets and suppositories) daily dose is 150 mg.

Diclofenac sodium is not recommended for use in patients under 16 years of age.

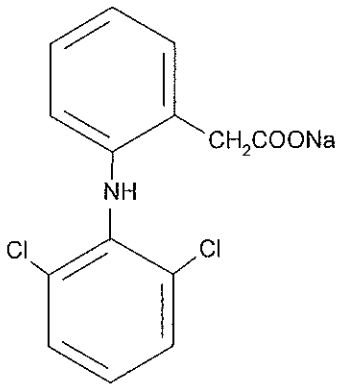
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Diclofenac Sodium

Chemical Name: 2-[(2,6-Dichlorophenyl)amine] benzene acetic acid, monosodium salt.

Structural Formula:



Description:	Diclofenac sodium is an almost white, hygroscopic crystalline powder. Freely soluble in water, insoluble in aqueous acid and in benzene.
pK_a	4.7
pH	between 6.0 and 8.0 (1% aqueous solution).

COMPOSITION

SANDOZ DICLOFENAC 50 mg: Each yellowish-white, torpedo-shaped suppository, with smooth surface, contains: diclofenac sodium 50 mg. Nonmedicinal ingredients: semi-synthetic glycerides.

SANDOZ DICLOFENAC 100 mg: Each yellowish-white, torpedo-shaped suppository, with smooth surface, contains: diclofenac sodium 100 mg. Nonmedicinal ingredients: semi-synthetic glycerides.

STABILITY AND STORAGE RECOMMENDATIONS

Protect suppositories from heat. Store between 15 and 30°C.

AVAILABILITY

SANDOZ DICLOFENAC 50 mg: Each suppository is individually wrapped in aluminum foil shells and available in boxes of 30.

SANDOZ DICLOFENAC, 100 mg: Each suppository individually wrapped in aluminum foil shells and available in boxes of 30.

INFORMATION FOR THE PATIENT

Your doctor has decided to use **SANDOZ DICLOFENAC** (diclofenac sodium) to treat your problem. Here are some things to know about diclofenac sodium in order to use it safely, and get the most benefit.

SANDOZ DICLOFENAC which has been prescribed to you by your doctor is one of a large group of nonsteroidal anti-inflammatory drugs (also called NSAIDs), and is used to treat the symptoms of certain types of arthritis such as rheumatoid arthritis and osteoarthritis including degenerative joint disease of the hip. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. NSAIDs do not cure arthritis, but they promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. This medicine will help you only as long as you continue to use it.

You should use **SANDOZ DICLOFENAC** only as directed by your doctor. Do not use more of it, do not use it more often and do not use it for a longer period of time than your doctor ordered. Using too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to use **SANDOZ DICLOFENAC** regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

UPSET STOMACH IS ONE OF THE COMMON PROBLEMS WITH NSAIDS

If upset stomach(indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

Do not use ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while using **SANDOZ DICLOFENAC** unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing

unwanted effects.

ALWAYS REMEMBER

The risks of using this medication must be weighed against the benefits it will have.

BEFORE USING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACISTS IF:

- You or a family member are allergic to or have had a reaction to diclofenac sodium or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diflunisal, fenoprofen, fluriprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);
- You or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);
- You have a history of upset stomach, ulcers, liver or kidney diseases;
- You have blood or urine abnormalities;
- You have high blood pressure;
- You have diabetes;
- You are on any special diet, such as a low-sodium or low-sugar diet;
- You are pregnant or intend to become pregnant while using this medication;
- You are breast feeding or intend to breast feed while using this medication;
- You are using any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin, digoxin, diuretics, oral hypoglycemic drugs, quinolone antibacterial drugs.
- You have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.
- You have any inflammatory lesions of the rectum or anus or if you have had rectal or anal bleeding recently.

WHILE USING THIS MEDICATION

- Tell any other doctor, dentist or pharmacist that you consult or see, that your are using this medication;
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or light-headed after taking this medication; some NSAIDs may cause drowsiness or fatigue in some people using them;
- Check with your doctor if you are not getting any relief of your arthritis or if any problems develop;
- Report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- Do not drink alcoholic beverages while using this medication. Stomach problems may be more likely to occur if you drink alcoholic beverages;
- Check with your doctor immediately if you experience unexpected weakness while using this medication, or if you vomit any blood or have dark or bloody stools;
- Some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;
- Check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;
- **Your regular medical checkups are essential.**

SIDE EFFECTS OF THIS MEDICATION

Along with its beneficial effects diclofenac sodium, like other NSAID drugs, may cause some undesirable reactions especially when used for a long time or in large doses.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side

Although not all of these side effects are common, when they do occur they may require medical attention.

CHECK WITH YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING ARE NOTED:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing, or tightness in the chest;
- skin rash, hives or swelling, itching;
- vomiting or persistent indigestion, nausea, stomach pain, diarrhea, rectal itching or bleeding;
- yellow discolouration of the skin or eyes;
- any change in the amount of or colour of your urine (dark red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- "flu-like" symptoms;
- tenderness just under your ribs on your right side;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, light-headedness;
- hearing problems.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

IDENTIFY YOUR MEDICATION

SANDOZ DICLOFENAC, 50 mg and 100 mg Suppositories: Each suppository, individually wrapped in aluminum foil shells, is torpedo-shaped with smooth surface and has a yellowish-white colour.

Check with your pharmacist if the colour appears different.

DOSING

How to use your medication: In order to receive optimum benefits from **SANDOZ DICLOFENAC** it is essential that you use it regularly as directed by your doctor. Use only the amount of medication at the time intervals and for as long as your doctor has prescribed it for. The maximum combined (tablets and suppositories) daily dosage for diclofenac sodium is 150 mg. A lower daily dosage may have been prescribed for you. Follow your prescribing instructions carefully.

If you are not getting adequate relief from your medication, speak to your doctor before you stop using it, as you may need up to 2 weeks to feel adequate relief.

SANDOZ DICLOFENAC, 50 and 100 mg suppositories, are individually wrapped in aluminum foil shells. Remove wrapping material before inserting the suppository into the rectum. Do not take suppositories by mouth. For ease of insertion, lubricate the tapered end of the suppository with cold water. Lie down on your side and use your finger to push the suppository as high as possible into the rectum. If it is felt that the bowels require emptying, this should be done before insertion of the suppository. If it is expelled, wash it off in cold water and re-insert. If the bowel needs to be emptied, this should be done before suppository insertion. If the suppository cannot be retained, discontinue use and consult a physician.

WHAT TO DO IF YOU MISS A DOSE

If you miss a dose take it as soon as you remember. If it is time for a scheduled dose then just take that one dose. Do not double-up your medication to compensate for the missed dose. **REMEMBER:** Do not take more than 150 mg of diclofenac sodium (tablets and suppositories) each day.

STORAGE

Protect suppositories from heat. Store between 15 and 30°C.

KEEP OUT OF THE REACH OF CHILDREN.

Diclofenac sodium is not recommended for use in patients under 16 years of age since safety and effectiveness have not been established.

Do not keep outdated medicine or medicine no longer needed.

This medication has been prescribed for your medical problem. Do not give it to anyone else.

If you require more information on this drug, consult your doctor or pharmacist.

PHARMACOLOGY

Diclofenac sodium is a phenyl-acetic acid derivative possessing anti-inflammatory, analgesic, and antipyretic activities as shown in various pharmacological models.

In-vitro diclofenac sodium does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Anti-inflammatory Activity in Rats

The anti-inflammatory potency was assessed by testing inhibition of paw edema (carrageenin solution and kaolin suspension) and reduction of adjuvant arthritis (Freund's adjuvant).

	Inhibition of edema induced by	
Preparation	Carrageenin (ED_{50} mg/kg) PO *	Kaolin (ED_{50} mg/kg) PO *
Diclofenac sodium	2.1	1.2

* determined by graphic interpolation from 3 or more doses.

Analgesic Activity in Mice and Rats

The antinociceptive effect of diclofenac sodium was assessed by established tests with results as tabulated.

	Analgesic Potency		
Preparation	Phenyl-*p*-benzoquinone test, mouse (ED_{50} mg/kg PO)	Acetic acid test, rat (ED_{50} mg/kg PO)	Ethacrynic acid test, rat (ED_{50} mg/kg PO)
Diclofenac sodium	4.3	2.5	1.4

Antipyretic Activity in Rats

Doses of 0.5 mg/kg PO diclofenac lowered body temperature by 1.5°C in rats given an IM injection of a 15% yeast suspension (10 mL/kg).

Inhibition of Prostaglandin

A close correlation exists between certain febrile reactions and increased prostaglandin levels in the brain. Diclofenac (0.5 mcg/mL) reduces prostaglandin E_2 formation which parallels antipyresis but does not induce hypothermia in the afebrile animal. The inhibition of prostaglandin synthesis *in vitro* (IC_{50} μM/L) is 1.6.

Platelet Adhesiveness

Diclofenac reduces collagen-induced aggregation in rabbit platelets by 50%, at 15 mcg/mL. ADP-induced adhesiveness at the same dosage is similarly affected. Diclofenac protected rabbits against the lethal action of thrombokinase without untoward effects, at 10 mg/kg PO.

Gastrointestinal Tolerability

In rats, oral doses of 17 mg/kg diclofenac sodium caused a blood loss of 150 μL in 72 hours, as measured by the administration of ^{51}Cr-labelled erythrocytes.

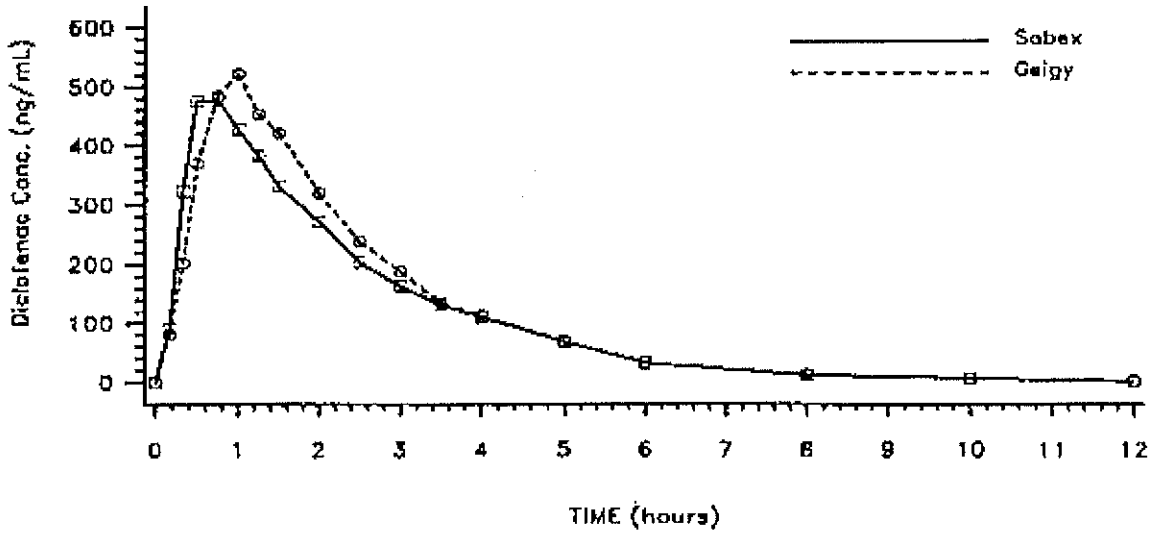
PHARMACOKINETICS

Bioavailability studies were performed, using normal human volunteers, on both the 50 mg and 100 mg SANDOZ DICLOFENAC suppository formulations. Each formulation was compared to either the corresponding 50 mg or 100 mg strength of Voltaren® suppository (Geigy). The results obtained are summarized as follows:

50 mg Suppository Formulation	SANDOZ DICLOFENAC (Sandoz)	Voltaren®(Geigy)	Bioavailability
$AUC_{(0\text{-}t)}$ (ng.hr/mL)	1172.7	1273.2	92%
$AUC_{(0\text{-}infinity)}$ (ng.hr/mL)	1220.1	1329.2	92%
C_{max} (ng/mL)	509.7	590.4	86%
T_{max} (hours)	0.82 (58)	1.09 (48)	----
$T_{1/2}$ (hours)	1.48 (53)	1.50 (51)	----
K_{el} ($hour^{-1}$)	0.5763 (41)	0.5546 (38)	----

The mean plasma diclofenac levels, shown below, demonstrate that both 50 mg formulations have similar absorption and elimination patterns, each peaking at approximately 1 hour.

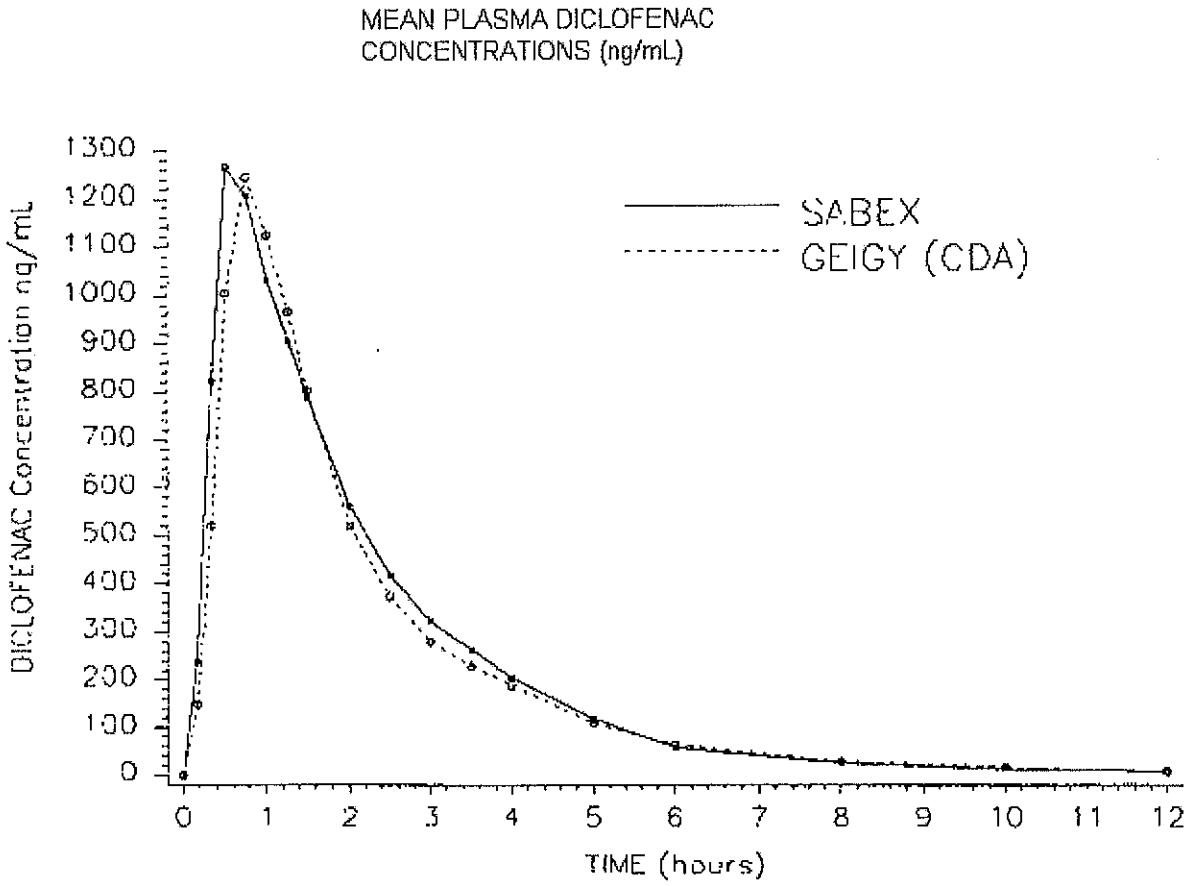
MEAN PLASMA Diclofenac CONCENTRATIONS (ng/mL)



The results of the comparison of the 100 mg SANDOZ DICLOFENAC suppository and the 100 mg Voltaren® suppository are as follows:

100 mg Suppository Formulation	**SANDOZ DICLOFENAC (Sandoz)**	**Voltaren® (Geigy)**	**Bioavailability**
$AUC_{(0\text{-}t)}$ (ng.hr/mL)	2624.2	2484.3	106%
$AUC_{(0\text{-infinity})}$ (ng.hr/mL)	2700.7	2601.9	104%
C_{max} (ng/mL)	1299.7	1284.1	101%
T_{max} (hours)	0.68	0.94	----
$T_{1/2}$ (hours)	1.63	1.84	----
K_{el} ($hour^{-1}$)	0.5458	0.4833	----

The mean plasma diclofenac levels, shown below, demonstrate that both 100 mg suppository formulations have similar absorption and elimination patterns, which peak at approximately 1 hour.



As the above results indicate, both the 50 mg and 100 mg SANDOZ DICLOFENAC suppositories are bioequivalent to the corresponding 50 mg or 100 mg Voltaren® (Geigy) suppository.

TOXICOLOGY

Acute Toxicity

Species	Route	LD_{50} mg/kg	95% Confidence Limits (mg/kg)
Mouse	PO IV	389 133	197 – 595 126 - 140
Rat	PO IV	173 106	133 – 213 80 - 132
Guinea-pig	PO IV	1110 127	950 – 1270 123 - 132
Rabbit	PO	194	151 - 259

The symptoms included bradycardia and convulsions.

The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequelae.

Long-Term Toxicity Studies

Species	Period	DAILY DOSE mg/kg/day PO		
		No signs of intoxication	Reversible signs of toxicity, mainly GI Tract	Minimum lethal dose
Rat	3 months 6 months 98 weeks	2 1 0.25	- 2 -	6 4 1
Dog	3 months	-	0.5	2
Rhesus Monkey	6 months	-	5-15	75
Baboon	12 months	-	5	10

Diclofenac sodium was given orally to male and female rats in doses of 0.25, 1.0 and 2.0 mg/kg/day from 59 weeks (high-dose groups) to 98 weeks (low- and intermediate-dose groups). High dose-related mortality rates resulted in termination of the high-dose administration after 59 weeks; the high mortality rate was caused by severe dose-dependent ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and sequelae. Body-weight gains

and feed consumption of the treated groups were close to the controls. Hematologic patterns showing neutrophilic leucocytosis and anemia were seen in the high- and intermediate-dose groups, particularly females at weeks 52 and 98, respectively. Female animals tended to develop enlarged adrenals and eventually experienced depressed glucose and elevated alkaline phosphatase levels. Histology studies carried out on the tissues of the control, low- and intermediate-dose groups showed drug-related changes including mucosal ulceration of the small intestine, lymphangiectasis, lymphoid hypoplasia, and plasma cell hypoplasia of the mesenteric lymph nodes, foci of hepatocytic hyperplasia, adrenal cortical atrophy and prostatitis. No increase in tumour incidence was observed in the drug-treated groups as compared to the control group.

Diclofenac sodium was administered orally in gelatin capsules once daily to baboons (*Papio spp.*) at dose levels of 0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day for up to 52 weeks. At all dose levels studied, diclofenac caused ulceration of the gastrointestinal tract. Ulceration was confined to the colon in the low-dose group but was present in the stomach and small intestine also in the other two groups. Body weights were below controls. Constipation, with occasional episodes of diarrhea, was a marked feature. In all treated groups, there was a dose-related fall in serum albumin levels. Anemia and an increased ESR were observed in the high-dose group. No intestinal lesions were present in the recovery groups (control, low and intermediate). Food consumption and body-weight gains were within normal limits. Hematology parameters were comparable to controls and serum albumin levels returned towards normal values.

Reproduction Studies

Rats: Doses of 2 and 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryotoxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated animals were comparable to those of controls except for slightly retarded growth at the higher dose.

Mice and Rats: Teratology studies at oral doses of 2, 3, 10 and 20 mg/kg/day showed no teratogenic effects on foetuses. At the higher doses, pronounced gastrointestinal effects were

observed in the dams and a marked toxic effect noted in foetuses (reduced birth weights and increased fetal deaths).

Rabbits: Pregnant females treated with oral doses of 5 or 10 mg/animal/day throughout the gestation period showed a dose-dependant increase in resorption rates, diminished fetus weights, and abnormal skeletal findings. Definite embryotoxicity was observed at the highest doses although there was no evidence to suggest teratogenicity.

Mutagenicity Studies

Mutagenicity studies were carried out *in vitro* using bacteria with, and without microsomal activation, and in mammalian cells. Studies *in vivo* were also performed. Diclofenac sodium was not mutagenic in any of these test systems.

Carcinogenicity Studies

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day have revealed no significant increases in tumour incidence. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats.

In a 2-year mouse study, only controls and animals at the two lower daily doses of 0.1 and 0.3 mg/kg showed survival sufficient for assessment of carcinogenic potential. The two higher daily doses of 1 and 2 mg/kg resulted in a shortening of lifespan, particularly in males, as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to nonsteroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. Diclofenac sodium was not carcinogenic to mice under the conditions of this study.

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